

PART II
PALLADIUM CATALYZED CASCADE REACTIONS OF ARYL
IODIDES, ALLENES, AND AMINES

CHAPTER 1

INTRODUCTION

Introduction

Palladium catalyzed reactions have been most widely investigated and proven extremely useful and advantageous in organic synthesis because they exhibit a high level of chemo-, regio-, and stereoselective transformations.^{1,2} Palladium salt and complexes are exceptionally versatile catalysts for construction of carbon-carbon and carbon-heteroatom bonds in carbocycles, heterocycles, 1,3-diens, enynes etc.³⁻⁵

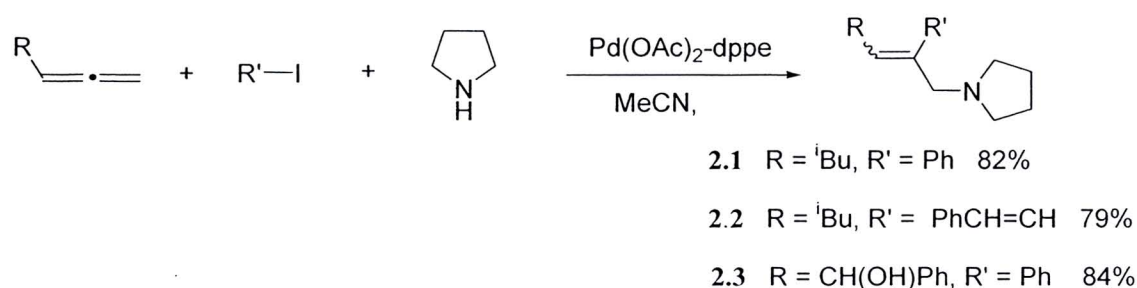
Cascade reactions have long attracted interest due to their many benefits including high atom economy, labor and waste saving attributes, and ability to rapidly access structurally complex compounds from relatively simple starting materials.^{6,7}

Cascade reaction is a multi-reaction sequences occurring in one pot where the functionality created in the first step allows the second step to proceed and so forth, the desired product is finally generated.

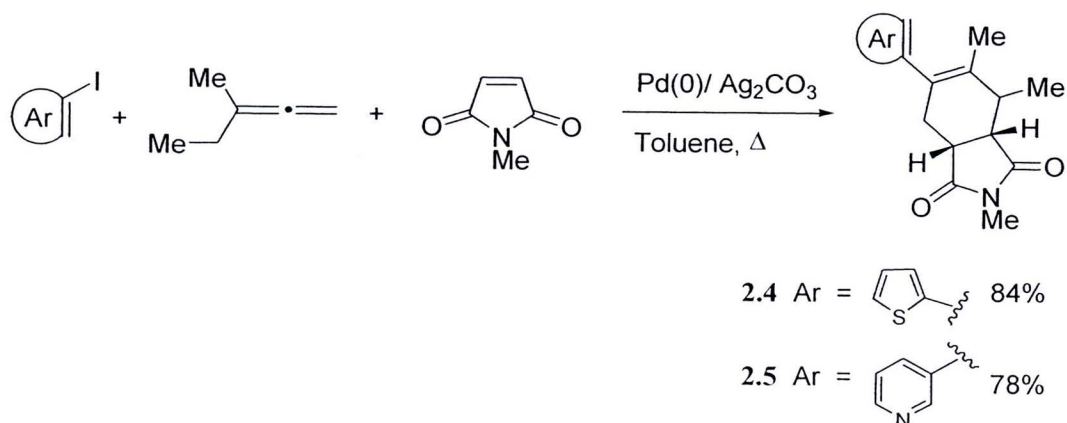
Three-component cascade reaction involving an aryl or heteroaryl iodide, an allene and a nucleophile (primary or secondary amine, amino acid methyl ester) are particularly interesting. It was found that incorporating the allene into the three-

component cascade process produced regio- and stereo-selective products. Stereodefined molecules containing this high level of functionality are not easy to synthesize by conventional methods.

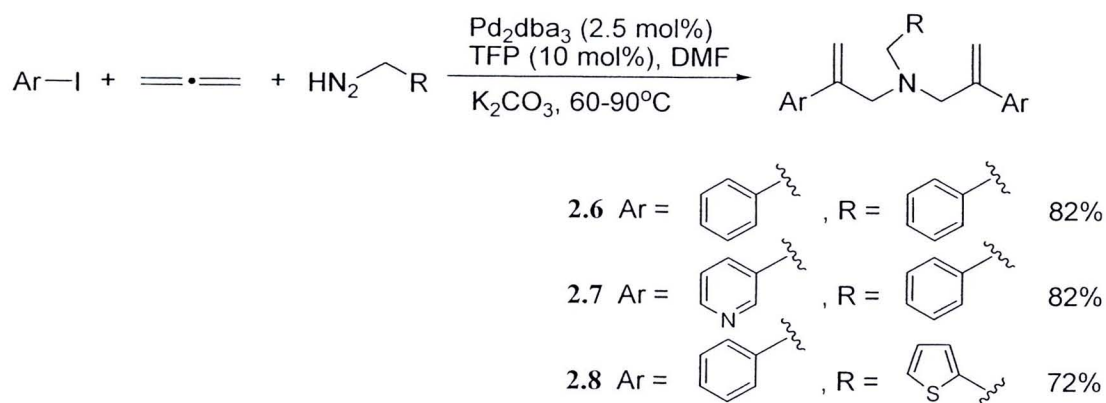
In 1984, Shimizu *et al.*⁸ reported the first palladium-catalysed 3-component cascade reaction of substituted allenes, phenyl iodides or alkyl bromides and secondary amine using by palladium acetate in the presence of 1,2 bis(diphenylphosphino)ethane in acetonitrile and obtained allylic amines (**2.1-2.3**) in 82-84% yield as a mixture of *E*- and *Z*- isomers.



In 1998, Grigg *et al.*⁹ reported the intermolecular Heck-Diels-Alder reactions of a wide variety of aryl/heteroaryl iodides with 1,1-dimethylallene and *N*-methylmaleimide to obtain 1,3-dienes. These cascades involved formation of three new bonds and one ring in moderate to good yield, as exemplified in compounds **2.4-2.5**.



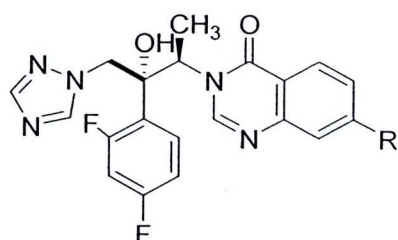
In 2001, Gai *et al.*¹⁰ synthesized bis(2-arylallyl) tertiary amine analogues, for example, compounds **2.6-2.8**, from aryl iodides, allene and primary aliphatic amines. The sequential transfer of two allyl groups from Pd(II) to a primary amine to form a tertiary amine in a one pot reaction had not been reported. The three-component reaction could be carried out under mild condition in the presence of a palladium catalyst in good yield and involved formation of two carbon carbon and two carbon-nitrogen bonds.



Biological Activity of Some Related Compounds

Pharmacologically, quinazolin-4-ones are among the most important classes of drug. Some derivatives of quinazoline (**2.9-2.12**) showed antifungal

activity against yeast and filamentous fungi with MIC_{50} value ranging from 0.3-3.5 $\mu\text{g/mL}$.¹¹ Compound **2.13** and **2.14** showed antimalarial activity with high selectivity against *P. falciparum* with EC_{50} values of 2.0×10^{-8} M.¹²

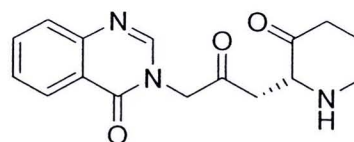


2.9 R = F

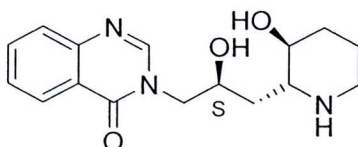
2.10 R = Cl

2.11 R = Br

2.12 R = I



2.13

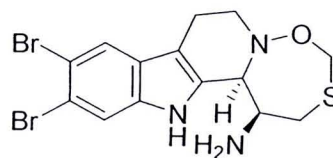


2.14

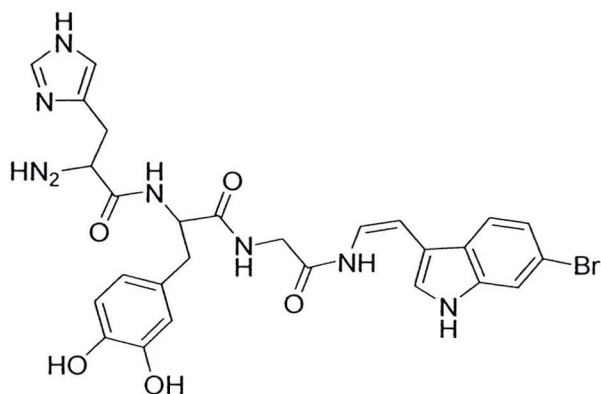
Indole is the precursor to many pharmaceuticals and found in a variety of natural products such as dragmacidin (**2.15**), eudistomin K (**2.16**), halocyanine A (**2.17**), and chelonin A (**2.18**) which showed cytotoxicity, antiviral, antibacterial, and anti-inflammatory activity, respectively.¹³



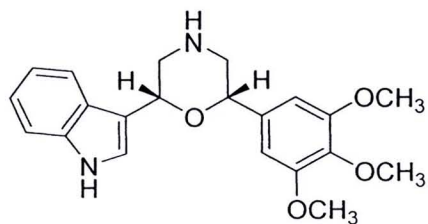
2.15



2.16

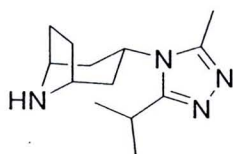


2.17

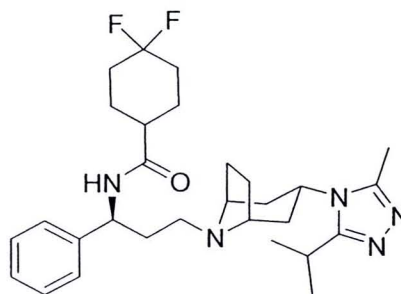


2.18

1,3,4-Triazole-substituted tropane (**2.19**) is a fragment of maraviroc (**2.20**) which used in the treatment of HIV infection.¹⁴

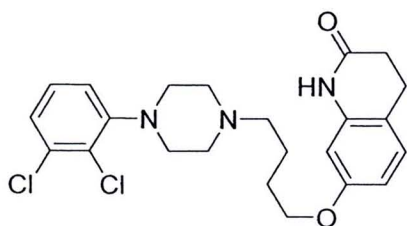


2.19

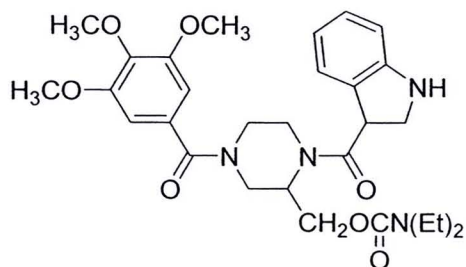


2.20

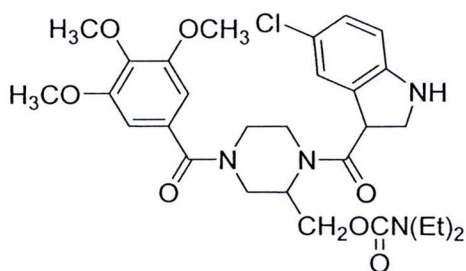
Piperazines are a broad class of chemical compounds, many with important pharmacological properties. Aripiprazole (**2.21**), a piperazine derivatives which contain a core piperazine functional group is an antidepressant used in the treatment of schizophrenia, bipolar disorder, and clinical depression.¹⁵ Compounds **2.22-2.23** showed anti-HIV with EC_{50} values of 4.5 and 7.3 μM , respectively.¹⁶



2.21



2.22



2.23

Due to the biological activities of these type of compounds, the syntheses of a trisubstituted olefin by three-component cascade reaction using an aryl iodide (5-iodoindole), quinazolinone allene and secondary amine (1,3,4-triazole-substituted tropane and piperazine) as starting material were therefore conducted with the hope to establish the products which may possess useful biological properties.